JACC Vol. 18, No. 7
December 1991:1602–9

Enalapril Versus Digoxin in Patients With Congestive Heart Failure: A Multicenter Study

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Patients with New York Heart Association functional class II or III heart failure stabilized on furosemide therapy were entered into a randomized controlled trial comparing enalapril (n = 72) and digoxin (n = 73). End points were clinical outcome, treadmill exercise capacity and echocardiographic left ventricular dimensions. Improvement in clinical outcome was defined as a reduction of at least one functional class, and deterioration as an increase of at least one functional class or withdrawal because of an adverse clinical event.

After 4 weeks, 13 patients receiving enalapril showed improvement, 55 had no change and 9 manifested deterioration compared with 7, 49 and 17, respectively, in the digoxin group ($p < 0.01$). After 14 weeks, 13 patients receiving enalapril showed improvement, 50 had no change and 9 manifested deterioration, compared with 14, 37 and 22, respectively, in the digoxin group ($p < 0.025$). More patients in the digoxin group were withdrawn because of an adverse clinical event ($p < 0.05$).

Exercise time and percent fractional shortening improved in both groups ($p < 0.001$ and <0.05, respectively), with no significant difference between groups ($p > 0.50$). Both rate-pressure product and subjectively evaluated exertion during submaximal exercise were reduced only in the enalapril group. Although the majority of patients in both groups did well, those receiving enalapril experienced fewer adverse clinical events and had less fatigue during submaximal exercise.

(J Am Coll Cardiol 1991;18:1602–9)

Angiotensin-converting enzyme inhibitors are effective therapy for patients with severe congestive heart failure and have been shown to both alleviate symptoms (1–5) and improve prognosis (6,7). Recent evidence (8) also shows that treatment with digoxin results in improvement in functional capacity and exercise time. Beaune (9) compared the efficacy of enalapril and digoxin in patients with heart failure and found no significant difference between the two agents. However, the inclusion of patients in functional classes I and IV and patients with atrial fibrillation complicates the interpretation of these results, as does the fact that ventricular function was not measured. The Captopril-Digoxin Multicenter Study (1) compared captopril, digoxin and placebo in patients with class II or III heart failure and showed a statistically significant clinical improvement with captopril but not digoxin. However, the degree of improvement in the digoxin group approached statistical significance and the study was unable to show a significant difference between the two drugs. Also, patients whose clinical status deteriorated during a baseline washout phase had to be excluded because of the possibility of randomization to placebo. This exclusion of digoxin responders potentially biases the study design against digoxin. The relative efficacy of angiotensin-converting enzyme inhibitors and digoxin in patients with heart failure receiving diuretic drugs therefore remains uncertain.

Our objective was to compare angiotensin-converting enzyme inhibitor therapy and digoxin in patients with functional class II or III heart failure, documented left ventricular dysfunction and normal sinus rhythm. We conducted a randomized, double-blind, parallel study in which patients initially stabilized on furosemide therapy were then randomized to receive either enalapril or digoxin. To minimize

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*A list of contributing investigators and participating centers appears in the Appendix.

Manuscript received February 25, 1991; revised manuscript received June 3, 1991, accepted June 24, 1991.

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0735-1097/91/$3.50

potential bias against digoxin, a placebo study arm was not included.

Methods

The study was conducted in the 12 Canadian centers listed in the Appendix and performed in compliance with the Medical Research Council of Canada guidelines concerning the protection of the rights and welfare of human subjects. The study received Ethics Committee Approval at all participating centers and all subjects provided written informed consent.

Eligibility. Clinically stable patients of either gender between the ages of 18 and 75 years with New York Heart Association functional class II or III symptoms of heart failure and evidence of left ventricular dysfunction documented within the previous 6 months were eligible for inclusion in the study. Criteria for left ventricular dysfunction were 1) end-diastolic diameter >6 cm or percent fractional shortening <25% on echocardiography, or 2) ejection fraction <50% on contrast or radionuclide angiography. In addition, eligible patients had documented physical signs or chest X-ray evidence of left heart dysfunction at some time in the past. The former included pulmonary rales or a third heart sound. The latter included a cardiothoracic ratio >0.50 or a transverse diameter of the heart exceeding the normal value for the patient's weight and height by >10% and signs of pulmonary venous hypertension.

Exclusion criteria included angiotensin-converting enzyme inhibitor use within the previous month; unstable angina, myocardial infarction or cerebrovascular accident within 3 months; hypertension (>160/95 mm Hg) or clinically important renal, hepatic or hematologic disorders; hemodynamically significant primary valvular or congenital heart disease; hypertrophic cardiomyopathy; atrial arrhythmias; predominant right-sided heart failure; the use of medications known to interact with digoxin (such as quinidine or amiodarone); concurrent use of cardiotonic or vasodilator drugs; a history of digoxin toxicity while taking appropriate doses of digoxin; contraindications to therapy with digoxin, furosemide or converting enzyme inhibitors; serum creatinine >1.5 mg/dl (130 mmol/liter) or blood urea nitrogen >25 mg/dl (8.3 mmol/liter); and any condition other than heart failure that could limit treadmill exercise tolerance (such as claudication, arthritis or orthopedic problems).

Study design. The study was a double-blind, parallel, multicenter clinical trial in which 145 patients whose condition had stabilized on treatment with furosemide plus placebo were then randomized to receive enalapril (n = 72) or digoxin (n = 73) for a treatment period of 14 weeks. The study consisted of a screening assessment period, a single-blind digoxin washout phase, a baseline assessment and randomization and clinical assessments after 4 and 14 weeks of therapy. After dose titration, patients received fixed doses of the study drugs unless a change was clinically indicated. All subjects in each group also received placebo for the alternative active medication.

Screening assessment. Study candidates underwent a screening assessment that included a medical history, physical examination and exercise treadmill testing using the modified Naughton protocol (10). To qualify, patients had to be capable of ≥6 but <18 min of treadmill exercise, with exercise tolerance limited by symptoms of heart failure such as fatigue or dyspnea. All patients were confirmed to be on a sodium-restricted (≤2 g total daily intake) diet and were maintained on the same diet throughout the study.

Washout of digoxin. Qualifying patients were withdrawn from active digoxin therapy and given an equivalent dose of digoxin placebo. Patients remained on their previous dosage of furosemide. Digoxin (or matching placebo) was supplied in 0.125-mg tablets and active furosemide in 20-mg tablets, with compliance verified at each visit by pill counts. All vasodilators, including long-acting nitrates, were withdrawn at that time. Patients returned after 1 week for a clinical assessment and diuretic dosage adjustment, if necessary. After a minimum of 2 weeks without digoxin therapy and with a constant and effective dosage of furosemide, patients returned for a baseline assessment.

Baseline assessment and randomization. The baseline assessment included a physical examination, two-dimensional echocardiogram and exercise treadmill test. Eligible patients were then randomized to receive either enalapril plus furosemide plus digoxin placebo (enalapril group) or digoxin plus furosemide plus enalapril placebo (digoxin group).

Titration of enalapril. Enalapril (or matching placebo) was administered at an initial dose of 5 mg twice daily. After the first dose, patients underwent continuous clinical monitoring with hourly blood pressure measurements for a minimum of 4 h until the blood pressure had stabilized. The dose was doubled every 2 weeks until one of the following occurred: 1) a 20% decrease in systolic pressure or a systolic pressure of 90 mm Hg; 2) a ≥10% decrease in systolic pressure after 1 min of standing; 3) symptoms of postural hypotension; or 4) the maximal dose of 20 mg twice daily was reached. If patients subsequently developed mild or moderate adverse effects possibly due to enalapril, the dose was reduced to the next lower level.

Titration of digoxin. The initial digoxin dose was based on body weight (≤50 kg = 0.125 mg; 51 to 79 kg = 0.25 mg; ≥80 kg = 0.375 mg), with adjustment by the investigator based on knowledge of patient age, renal function and other variables that might affect digoxin clearance. After 2 weeks of stable doses of digoxin or matching placebo, a trough plasma sample was sent to a core laboratory (Ottawa Civic Hospital) for analysis. Clinical centers were advised regarding the appropriate dose adjustment when plasma levels were outside the therapeutic range (1 to 2 nmol/liter). An equivalent number of digoxin placebo dose adjustments were randomly made in the enalapril group to maintain the double-blind protocol. If signs or symptoms consistent with mild digoxin toxicity developed, the dose of digoxin or

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digoxin placebo was reduced without obtaining a plasma level. If signs or symptoms consistent with potentially serious digoxin toxicity developed, the patient was withdrawn from the study and appropriate therapy started.

Furosemide adjustment. Investigators adjusted the dose of furosemide as clinically indicated. The dose was decreased if significant or symptomatic postural hypotension occurred and was increased if signs or symptoms of worsening pulmonary congestion developed. The maximal daily dose was 120 mg. The dose of furosemide given during the baseline period was maintained throughout active treatment unless a change was clinically indicated.

Potassium supplementation. Supplemental potassium was withdrawn at the time of randomization. Serum potassium levels were measured at every visit and supplemental potassium was prescribed if levels were <3.5 mmol/liter.

Clinical assessments. Clinical assessments consisted of a medical history, physical examination and determination of New York Heart Association functional classification. Assessments were made at the beginning of the single-blind digoxin washout period (screening), immediately before randomization (baseline) and after 4 and 14 weeks of therapy.

Exercise testing. Treadmill exercise capacity was assessed with use of the modified Naughton protocol at screening, baseline and weeks 4 and 14. Tests were scheduled at the same time of day (±1 h) and ≥2 h after a light meal. A standard set of instructions was read at the beginning of each treadmill test and a uniform amount of encouragement given to each patient. Subjects graded the amount of perceived exertion after each stage of the exercise protocol and at peak exercise using the 10-point Borg scale (11). A patient was randomized only if the limiting factor for exercise was fatigue or dyspnea.

Echocardiography. Two-dimensional echocardiograms were obtained at screening, baseline and weeks 4 and 14. These were done before exercise testing at the same time of day (±1 h) for individual patients. The following measurements were recorded: left ventricular internal diameter at end-diastole, left ventricular internal diameter at end-systole and E point to septal separation. Percent fractional shortening of the left ventricle was calculated by the following formula:

$$100\ (\text{End-diastolic diameter} - \text{End-systolic diameter}) / \text{End-diastolic diameter}.$$

Clinical chemistry values and hematology. Laboratory determinations were obtained at screening, baseline and weeks 4 and 14. These included a complete blood count with differential and platelet determination and measurement of serum electrolytes, bilirubin, creatine kinase, hepatic enzymes, total protein, albumin and uric acid. Additional electrolyte determinations were made 1 week after the start of the study medication and at 2-week intervals during maintenance therapy.

Statistical Analysis

End points. The planned primary end points were 1) clinical outcome and functional capacity, 2) treadmill exercise capacity, and 3) change in echocardiographic dimensions. Significantly more patients in the digoxin group were withdrawn from the study because of clinical worsening, a factor that potentially prejudices end points 2 and 3 against enalapril. End point 1 includes patients withdrawn because of clinical events and is therefore less subject to bias. Secondary end points were the rest and exercise heart rate, blood pressure, rate-pressure product (heart rate × systolic blood pressure) and the change in rating of perceived exertion after each exercise stage. A two-tailed alpha of ≤ 0.05 was considered statistically significant.

Change in clinical outcome and functional capacity. Clinical improvement was defined as a reduction in functional class of at least one category. Clinical worsening was defined as either an increase in functional class of at least one category or the occurrence of an adverse clinical event of sufficient severity to require withdrawal from the study. Groups were compared by contingency table analysis with use of the chi-square statistic with the Yates correction or the Fisher exact test as appropriate. The primary analysis included the 145 patients completing the study or withdrawing because of an adverse clinical event. Eight patients who withdrew for nonclinical reasons were not included in this analysis; this group comprised three patients who were noncompliant with study medications, one who was withdrawn by his family doctor for unspecified reasons and four who withdrew because of geographic considerations. To guard against potential bias, we also conducted a separate analysis including these patients.

Change in treadmill exercise time. Univariate repeated measures analysis of variance was used to evaluate change in exercise tolerance. Groups were compared with use of data obtained at baseline and at weeks 4 and 14.

Echocardiographic dimensions. Changes in echocardiographic dimensions were evaluated by using paired *t* tests to compare measurements obtained at weeks 4 and 14 with baseline values.

Change in rating of perceived exertion during exercise. Patients rated the amount of exertion perceived subjectively after each exercise stage using the 10-point Borg scale (11). Results obtained from patients completing study weeks 4 and 14 were compared with individual baseline values by using paired *t* tests. This procedure avoided any bias that would have been caused by including baseline data from patients subsequently withdrawn from the protocol.

Change in rest and exercise heart rate, blood pressure and rate-pressure product. Heart rate and blood pressure were measured at rest, after each exercise stage and at peak exercise. Rate-pressure product was calculated as the product of heart rate and systolic pressure. Results obtained from patients completing study weeks 4 and 14 were compared with individual baseline values by using paired *t* tests. This

Table 1. Clinical Characteristics of 145 Randomized Patients

	Enalapril	Digoxin
Baseline		
No.	72	73
Age (yr)	59 ± 8	59 ± 9
Male/female	58/14	51/22
Previously receiving digoxin (yes/no)	43/29	44/29
Previously receiving furosemide (yes/no)	54/18	52/21
Prior furosemide dose (mg/day)	49 ± 24	43 ± 23
Cardiothoracic ratio	0.53 ± .08	0.51 ± 0.06
Rest HR (beats/min)	84 ± 13	88 ± 16
Exercise duration (s)	730 ± 209	665 ± 204
NYHA class (II/III)	48/24	46/27
S_3 present/absent	36/36	37/35
Left atrium (mm)	42 ± 6	43 ± 8
LV diastolic diameter (mm)	66 ± 7	67 ± 8
LV systolic diameter (mm)	55 ± 9	57 ± 9
E point to septal separation (mm)	21 ± 10	22 ± 9
Radionuclide ejection fraction (%)*	28 ± 13	31 ± 12
Serum sodium (mmol)	141 ± 2.9	141 ± 3
Serum potassium (mmol)	4.1 ± 0.4	4.1 ± 0.4
Serum creatinine (mmol)	1.2 ± 0.2	1.1 ± 0.2
Etiology: ischemic†/idiopathic	52/16	46/25
Etiology: hypertensive/corrective valvular	3/1	1/1
Postrandomization		
Enalapril (mg/day) (range)	19 (10–40)	
Digoxin (mg/day) (range)		0.284 (0.125–0.5)
Furosemide (mg/day) (range)	44.7 (10–160)	49.2 (20–160)

*n = 36 and 42 in the enalapril and digoxin groups, respectively. †Previous myocardial infarction or coronary angiogram showing >70% stenosis in at least one proximal coronary artery. HR = heart rate; LV = left ventricular; NYHA class = New York Heart Association functional class; S_3 = third heart sound.

avoided any bias that would have been caused by including baseline data from patients subsequently withdrawn from the protocol.

Results

Patient characteristics (Table 1). One hundred fifty-five patients entered screening; 10 of these patients were withdrawn, two for worsening heart failure during digoxin wash-out, and 8 after randomization for reasons other than clinical deterioration. Thus, 145 patients (109 men, 36 women) were included in the primary analysis. The average age was 59 ± 15 years and the average weight 77 ± 15 kg. The treatment groups were well matched, with no significant differences between groups in baseline characteristics. The mean steady state plasma digoxin level in the digoxin group was 1.26 ± 0.43 nmol/liter. Digoxin levels were undetectable in the enalapril group.

Table 2. Clinical Outcome at Weeks 4 and 14 in 145 Patients Taking Enalapril or Digoxin

	Week 4		Week 14	
	Enalapril	Digoxin	Enalapril	Digoxin
Improvement	13 (18%)	7 (10%)	13 (18%)	14 (19%)
No change	55 (76%)	49 (67%)	50 (69%)	37 (51%)
Worsening	4 (6%)	17 (23%)	9 (13%)	22 (30%)
Total	72	73	72	73

Improvement is defined as lowering of New York Heart Association functional class, worsening as an increase in functional class or discontinuation because of an adverse clinical event. (Week 4 chi-square = 10.19, $p < 0.01$; week 14 chi-square = 7.43, $p < 0.025$.)

Table 3. Reason for Discontinuation of Therapy in Randomized Patients

	Enalapril	Digoxin	Total
Symptoms of CHF	2	7	9
Other cardiac causes*	2	5	7
Azotemia	1	1	2
Other noncardiac causes†	2	5	7
Total	7	18	25

*Enalapril group: hypotension, ischemia. Digoxin group: atrial fibrillation, palpitation, hypertension, ischemia (n = 2). †Enalapril group: anorexia and loss of taste, transient ischemic attack. Digoxin group: muscle cramps and hyperglycemia, rash, headache and vertigo, nausea and vomiting, pulmonary neoplasm. CHF = congestive heart failure.

Change in clinical outcome and functional capacity (Tables 2 to 4). We observed significant differences in clinical outcome between the groups treated with enalapril or digoxin in favor of the enalapril group after both 4 and 14 weeks of therapy (Table 2). An "intention to treat analysis" that included all patients withdrawn for any reason produced similar results (week 4: chi-square = 13.98, df = 2, p = 0.001; week 14: chi-square = 7.32, df = 2, p = 0.026). If only patients withdrawn for definite symptoms of heart failure are included, the difference between groups is statistically significant at week 4 ($p < 0.03$), but not at week 14 ($p = 0.08$).

Twenty-five patients (17%) withdrew prematurely because of an adverse clinical event. More patients in the digoxin group withdrew by week 4 (13 of 73 vs. 4 of 72, p = 0.037 [Fisher's exact test]) and week 14 (18 of 73 vs. 7 of 72, p = 0.027 [Fisher's exact test]). Table 3 shows the reasons for withdrawal from the study. Table 4 shows that these

Table 4. Comparison of Baseline Characteristics of Patients Who Did or Did Not Withdraw From the Study Because of Adverse Clinical Events

	Withdrawal From Study		
	Yes (n = 25)	No (n = 120)	p Value
Age (yr)	58 ± 11	59 ± 9	NS
Exercise tolerance (s)	576 ± 193	725 ± 202	<0.001
NYHA class II/III	11/14	83/37	<0.05
S_3 present/absent	10/15	60/60	NS
LVEDD (mm)	66 ± 8	67 ± 8	NS
LVESD (mm)	55 ± 8	56 ± 9	NS
Rest HR (beats/min)	93 ± 16	85 ± 14	<0.025

LVEDD and LVESD = left ventricular internal diameter at end-diastole and end-systole, respectively; other abbreviations as in Table 1.

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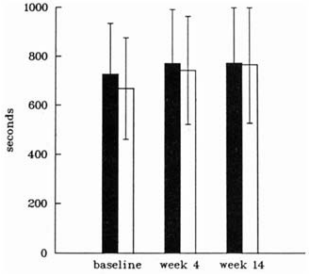

Figure 1. Maximal treadmill exercise capacity (time). Both treatment groups showed significant improvement, with no significant difference between the digoxin (**white bars**) and enalapril (**black bars**) groups. Comparison is biased because of the many patients who withdrew from the digoxin group. **Error bars** represent standard deviation.

patients tended to be in functional class III rather than class II, with poorer baseline exercise tolerance and higher heart rate at rest.

Change in maximal exercise capacity. Figure 1 shows maximal treadmill exercise capacity for the digoxin and enalapril groups at baseline and weeks 4 and 14. Both the enalapril and digoxin groups showed significant improvement ($p < 0.001$), with no difference between groups ($p = 0.497$).

Echocardiographic dimensions (Table 5). Both groups showed significant decreases in internal left ventricular systolic dimension at week 14 and a resulting increase in percent fractional shortening. There was no significant change in other atrial and ventricular dimensions and no significant differences between groups.

Change in rating of perceived exertion during exercise. Figure 2 shows the change in rating of perceived exertion from baseline after each exercise stage at weeks 4 and 14. There were significant reductions in the enalapril group, with no significant change observed in the digoxin group.

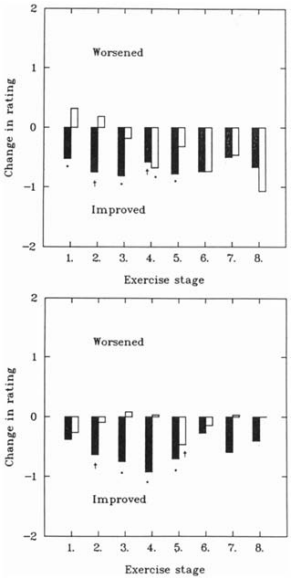

Figure 2. Change in rating of perceived exertion during exercise at week 4 (**top**) and week 14 (**bottom**). **White bars** indicate the digoxin group and **black bars** the enalapril group. *$p < 0.05$; †$p < 0.01$.

Change in rest and exercise heart rate, blood pressure and rate-pressure product (Fig. 3). The results were similar for patients completing week 4 and week 14. The enalapril group showed the expected decrease in systolic and diastolic blood pressure at rest, with no change in heart rate at rest. The

Table 5. Echocardiographic Measurements in the Enalapril and Digoxin Groups

	Enalapril			Digoxin		
	Baseline	Week 4	Week 14	Baseline	Week 4	Week 14
Left atrium (mm)	42 (6)	41 (7)	41 (7)	43 (7)	43 (7)	42 (7)
LVEDD (mm)	66 (7)	66 (8)	66 (8)	67 (8)	66 (8)	66 (10)
LVESD (mm)	55 (9)	55 (9)	53 (10)*	57 (10)	55 (10)	54 (12)†
% fractional shortening	15 (10)	17 (7)	20 (10)†	15 (5)	15 (9)	20 (7)*
EPSS (mm)	22 (10)	21 (9)	21 (9)	23 (9)	23 (7)	23 (8)

*$p < 0.01$; †$p < 0.05$. Values are mean values ± SD (in parentheses). EPSS = E point to septal separation; other abbreviations as in Table 4.

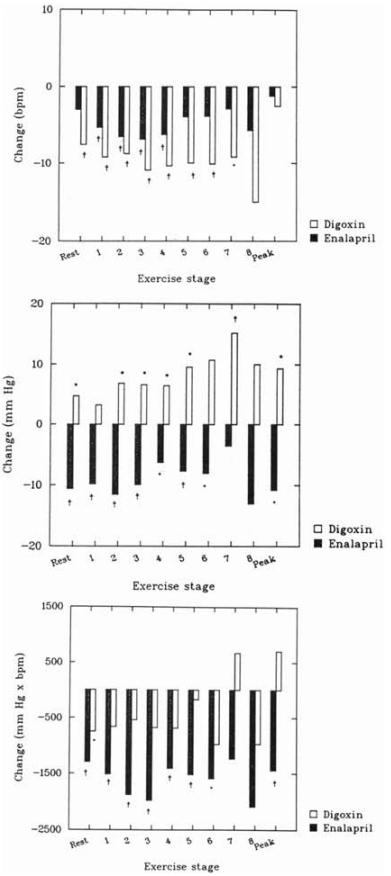

Figure 3. Change in rest and exercise values at week 14 for heart rate **(top)**, systolic blood pressure **(center)** and rate-pressure product (heart rate × systolic blood pressure). **White bars** indicate the digoxin group and **black bars** the enalapril group. *$p < 0.05$; †$p < 0.01$.

digoxin group showed a slight increase in systolic blood pressure and a significant decrease in heart rate. The reduction in rate-pressure product was significant in both groups but greater in the enalapril group.

The enalapril group showed a significant reduction in systolic and diastolic blood pressure after each exercise stage and at peak exercise. In the digoxin group systolic blood pressure increased but there was no change in diastolic pressure. Heart rate decreased in both groups at intermediate exercise stages but the magnitude of the decrease was greater in the digoxin group. The enalapril group showed a significant reduction in rate-pressure product at intermediate exercise stages and peak exercise; a smaller reduction in the digoxin group did not reach statistical significance.

Safety. There were no deaths during the study. Azotemia developed in two patients (one in each group). Otherwise, there were no clinically significant changes in routine hematologic or clinical chemistry measures.

Discussion

Enalapril versus digoxin. In the present study, among patients with heart failure whose condition had stabilized on diuretic drug therapy, those receiving additional therapy with an angiotensin-converting enzyme inhibitor had a better short-term clinical outcome and experienced less fatigue during submaximal exercise than did those receiving digoxin. However, there was no difference in the degree of improvement in either treadmill exercise capacity or left ventricular function between the groups receiving enalapril and digoxin. After 4 weeks of treatment, more patients receiving enalapril had improved functional class, whereas after 14 weeks, the enalapril and digoxin groups were equivalent in this regard. More patients in the digoxin group showed deterioration at both 4 and 14 weeks of therapy, primarily because of a high withdrawal rate before the week 4 evaluation. It is unlikely that this difference was due to chance because the treatment groups were well matched with regard to baseline characteristics and the results were essentially unchanged in an intention to treat analysis that included patients withdrawn for nonclinical reasons.

The treatment effects after 14 weeks of therapy were modest, with 18% to 19% of patients in each group showing clinical improvement. The difference between the two groups at that time was due to the greater number of patients in the digoxin group who withdrew from the study before 4 weeks. One possible explanation for these findings may be that the beneficial effects of digoxin are delayed compared with those of enalapril. Such a delay would explain why more patients in the enalapril group showed improvement at week 4 but not at week 14, as well as why early withdrawal was more frequent in the digoxin group. Patients withdrawn because of clinical worsening were more likely to be in functional class III and had poorer baseline exercise tolerance. This observation is consistent with the improved

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functional capacity seen in the patients in class IV receiving enalapril in the CONSENSUS Trial (6).

Previous studies. Two previous large studies (1,9) did not show significant differences between angiotensin-converting enzyme inhibitors and digoxin in the treatment of patients with heart failure. However, both studies had important limitations. Beaune (9) conducted a randomized double-blind comparison of enalapril and digoxin in heart failure and reported no difference between the two agents. These results are difficult to interpret because that study did not measure left ventricular function and included patients with atrial fibrillation as well as patients with class I and IV heart failure. The other study (1), a randomized, double-blind, placebo-controlled comparison of captopril and digoxin, found a significant difference between placebo and captopril but not between placebo and digoxin. However, the patients randomized to digoxin showed improvement of a magnitude that was similar to that of patients receiving captopril and closely approached statistical significance. There was no statistically significant difference between the active treatment groups. In that study a significant number of patients showed clinical deterioration during washout of digoxin and were withdrawn from the study before randomization, thus creating a potential bias in favor of captopril by the selective exclusion of digoxin responders. In the present study, only two patients were excluded before randomization because of worsening heart failure, a number unlikely to effect the overall result. One possible reason for the lower dropout rate in our study is the absence of a placebo group. Because there was no possibility of being randomized to inactive therapy, those patients showing mild deterioration whose condition stabilized with diuretic therapy did not have to be withdrawn during the baseline phase.

Exercise tolerance. The major limitation of a comparison of two active agents without a placebo group is that it does not allow an independent assessment of the efficacy of the individual agents. Other studies have shown the efficacy of enalapril (12,13) and digoxin (8,14) individually. We found no significant difference between the enalapril and digoxin groups in the amount of improvement in maximal treadmill exercise capacity. Although this capacity improved in both groups, this result is difficult to interpret in the absence of a placebo group. The comparison of maximal exercise capacity between the two groups may have been biased against enalapril because of the withdrawal of patients with severe heart failure from the digoxin group. The digoxin group would likely have shown less improvement had these patients remained in the study.

The enalapril group showed a significant reduction in the patients' subjective rating of perceived exertion, but the digoxin group did not. This outcome occurred even though the selective withdrawal of patients with more severe heart failure from the digoxin group would also tend to bias this comparison in favor of the digoxin group. Because the cardiac work loads at intermediate exercise stages are more similar to those occurring during usual daily activities, the rating of perceived exertion at lower levels of exercise may have more clinical relevance than does maximal exercise capacity.

Echocardiographic dimensions. Percent fractional shortening improved in both the enalapril and digoxin groups. The decrease in systolic blood pressure in the enalapril group suggests that improved ventricular function is a consequence of decreased cardiac afterload, whereas the increase in this variable in the digoxin group is consistent with the positive inotropic effect of this agent.

Effects on heart rate, blood pressure and cardiac work load. As anticipated, enalapril reduced both systolic and diastolic blood pressure at rest, after each intermediate exercise stage and at peak exercise. There was also a small reduction in exercise heart rate. The net effect was to reduce the rate-pressure product both at rest and with exercise. In contrast, digoxin caused a significant decrease in rest and exercise heart rate and a significant increase in rest and exercise systolic blood pressure. The net effect was no significant change in rate-pressure product during exercise and a small but significant reduction at rest. The reduced work loads at intermediate exercise stages in the enalapril group were associated with a reduction in the rating of perceived exertion. Further research will determine if there is a cause and effect relation.

The effect of enalapril on cardiac work load at rest and during exercise is consistent with its generally recognized mechanism of action, that of an afterload-reducing agent. It is likely that the reduction in myocardial work load has a long-term beneficial effect on myocardial function. Digoxin also caused a reduction in myocardial work load at rest as a result of its depressant effect on heart rate. Recent data showing a relative inefficacy of more potent positive inotropic agents (8,15–18) suggest that positive inotropism by itself may not be sufficient to produce long-term benefits. The negative chronotropic effect of digoxin, by reducing cardiac work load, may be at least partially responsible for its long-term efficacy.

Clinical significance. It is now well appreciated that it is extremely difficult to assess the effects of drugs for the treatment of congestive heart failure because of the difficulty in selecting end points that are clinically meaningful, other than their effects on long-term mortality. In the present study, after stabilization on diuretic therapy, the majority of patients receiving either enalapril or digoxin had a similar degree of improvement in maximal treadmill exercise capacity and left ventricular function and no change in functional class. However, those patients receiving enalapril experienced a better short-term clinical outcome and more subjective improvement in treadmill exercise tolerance at submaximal work loads. The relation between these end points and long-term prognosis is not known. However, a reduction in perceived exertion at work loads representative of those occurring during usual activities may improve the quality of life and functional capacity. Compared with enalapril, digoxin has a more marked negative chronotropic effect and

increases rather than decreases systolic blood pressure. The complementary hemodynamic effects of the agents suggests that they may be beneficial in combination. Clinical trials that are now being initiated will determine the long-term utility of this approach.

Appendix

Canadian Enalapril Versus Digoxin Study Group

Clinical Centers

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We gratefully acknowledge the assistance of Margaret Herbert and Heather Morrisette in data collection.

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